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## Potential Intussusception Risk Versus Benefits of Rotavirus Vaccination in the United States

Rishi Desai, MD, MPH, Margaret M. Cortese, MD, Martin I. Meltzer, PhD, Manjunath Shankar, MB, BS, PhD, Jacqueline E. Tate, PhD, Catherine Yen, MD, MPH, Manish M. Patel, MD, and Umesh D. Parashar, MB, BS, MPH

Centers for Disease Control and Prevention, Atlanta, GA

### Abstract

**Background**—International data show a low-level increased risk of intussusception associated with rotavirus vaccination. Although US data have not documented a risk, we assumed a risk similar to international settings and compared potential vaccine-associated intussusception cases with benefits of prevention of rotavirus gastroenteritis by a fully implemented US rotavirus vaccine program.

**Methods**—To calculate excess intussusception cases, we used national data on vaccine coverage and baseline intussusception rates, and assumed a vaccine-associated intussusception relative risk of 5.3 (95% confidence interval [CI]: 3.0–9.3) in the first week after the first vaccine dose, the risk seen in international settings. We used postlicensure vaccine effectiveness data to calculate rotavirus disease burden averted.

**Results**—For a US birth cohort of 4.3 million infants, vaccine-associated intussusception could cause an excess 0.2 (range: 0.1–0.3) deaths, 45 (range: 21–86) hospitalizations and 13 (range: 6–25) cases managed in short-stay or emergency department settings. Vaccination would avert 14 (95% CI: 10–19) rotavirus-associated deaths, 53,444 (95% CI: 37,622–72,882) hospitalizations and 169,949 (95% CI: 118,161–238,630) emergency department visits. Summary benefit–risk ratios for death and hospitalization are 71:1 and 1093:1, respectively.

**Conclusions**—The burden of severe rotavirus disease averted due to vaccination compared with the vaccine-associated intussusception events offers a side-by-side analysis of the benefits and potential risks. If an intussusception risk similar to that seen internationally exists in the United States, it is substantially exceeded by the benefits of rotavirus disease burden averted by vaccination.

### Keywords

rotavirus; vaccine; United States; risk; intussusception

Address for correspondence: Rishi Desai, MD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, MS-A34, Atlanta, GA, 30333. rdesai1@cdc.gov.

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Before the introduction of rotavirus vaccine in 2006, rotavirus gastroenteritis annually caused approximately 20–60 deaths, 55,000–70,000 hospitalizations and 200,000 emergency department (ED) visits among US children aged <5 years.<sup>1</sup> Since implementation of 2 rotavirus vaccines, a pentavalent rotavirus vaccine (RV5; RotaTeq, Merck and Co., Whitehouse Station, NJ) and a monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals, Philadelphia, PA), healthcare utilization for rotavirus gastroenteritis among US children has dramatically fallen.<sup>2–5</sup>

A previous rotavirus vaccine, RotaShield (Wyeth, New York, NY) was withdrawn from the US market in 1999 after being associated with an ~30-fold increased risk of intussusception, a potentially life-threatening intestinal blockage, in week 1 after dose 1.<sup>6</sup> Prelicensure trials of >60,000 infants each<sup>7,8</sup> did not find an increased intussusception risk for all doses combined within a window of 42 days after each of 3 RV5 doses or 30 days after each of 2 RV1 doses. Postlicensure evaluations of RV1 in Mexico, however, have identified a low-level (~5-fold) increased risk of intussusception in week 1 after dose 1.<sup>9</sup> After the introduction of the vaccine, active surveillance for infants with intussusception was performed at 16 hospitals, and vaccination records were obtained on cases and age-matched neighborhood controls. The findings were similar using the self-controlled case series and case control methods. In Australia, a possible risk was identified with both RV5 and RV1,<sup>10</sup> although based on small numbers of intussusception cases. In this evaluation, active surveillance for intussusception was performed after the introduction of the vaccine, rotavirus vaccination data were obtained and the number of cases observed postintroduction was compared with the number expected based on historical intussusception rates. Available US data are insufficient to exclude a risk of the magnitude seen in these international settings.<sup>11–14</sup>

To inform clinicians and parents of the risk and benefits of rotavirus vaccine, we estimated the potential number of vaccine-associated intussusception cases in the United States, assuming a risk of intussusception similar to that measured internationally exists. We then compared that risk with cases of rotavirus disease averted by vaccination.

## METHODS

We built 2 probabilistic Monte Carlo models. The first Monte Carlo model (model 1) estimated the number of rotavirus-associated deaths, hospitalizations and ED visits that would occur in a US birth cohort followed to age 5 with and without a rotavirus vaccine program. For model 1, we used diphtheria and tetanus toxoid and acellular pertussis (DTaP) vaccine coverage data to estimate the coverage achievable with rotavirus vaccine in a fully matured rotavirus vaccine program. The second Monte Carlo model (model 2) estimated benefit–risk ratios using the estimates from model 1 of the number of rotavirus deaths, hospitalizations and ED visits averted by rotavirus vaccine and the number of intussusception deaths, hospitalizations and ED visits potentially caused by vaccine. The number of intussusception cases potentially caused by vaccine was derived by using baseline intussusception rates in the United States, the number of infants in the cohort who would receive rotavirus vaccine in a fully mature program and the relative risk of vaccine-associated intussusception found in Mexico (point estimate, 5.3).<sup>9</sup> We then used benefit and

risk data to determine the rate of rotavirus hospitalization and intussusception for an individual infant. Finally, we performed a sensitivity analysis to examine the impact of changing the estimate of relative risk of vaccine-associated intussusception on the ratio of rotavirus events averted by vaccine to intussusception events potentially caused by vaccine.

### Model 1: Rotavirus Disease Burden With and Without Rotavirus Vaccination

We used a previously published Monte Carlo probabilistic model to estimate, for a US birth cohort of 4,261,494 infants modeled to 5 years of age, the rotavirus disease burden with and without a fully implemented rotavirus vaccine program.<sup>15</sup> The difference in rotavirus disease burden (deaths, hospitalizations and ED visits) with and without vaccine represents vaccine benefits. Because RV5 accounted for more than 90% of all US rotavirus vaccinations from February 2006 through August 2010,<sup>12</sup> we used in model 1 estimates of rotavirus vaccine coverage in a fully mature program and vaccine effectiveness based on the 3-dose RV5 vaccine. We used triangular probability distributions of vaccine effectiveness against death/hospitalization and ED visits due to rotavirus disease (Table 1) and incorporated data on DTaP vaccine coverage to estimate the rotavirus vaccine coverage achievable.

**Rotavirus Vaccine Effectiveness**—Vaccine effectiveness estimates for full and partial immunization schedules to age 5 are based on data on RV5 effectiveness from a large postlicensure study. For a full 3-dose vaccine series, vaccine effectiveness for rotavirus gastroenteritis hospitalization was estimated at 92% (95% confidence interval [CI]: 86–96%), with partial immunization with only 2 or 1 doses of rotavirus vaccine conferring 90% (95% CI: 75–97%) and 66% (95% CI: 16–86%) effectiveness, respectively.<sup>16</sup> We assumed the vaccine effectiveness against rotavirus-associated death to be the same as the effectiveness against rotavirus hospitalization. For effectiveness against ED care for rotavirus disease, we used a 3-dose effectiveness of 81% (95% CI: 53–92%).<sup>16</sup> Because published data on effectiveness of a partial series of RV5 against ED visits for rotavirus are not available, effectiveness for 1 or 2 doses of rotavirus vaccine for preventing ED visits was obtained by taking an absolute reduction of 11 percentage points (the difference in 3-dose vaccine effectiveness between hospitalization and ED care) from the respective 1- or 2-dose effectiveness estimates against hospitalization (Table 1). Although data from the single largest study to date were used, the full and partial series effectiveness estimates from this study are similar to those from other published US RV5 effectiveness evaluations.<sup>17,18</sup>

**Rotavirus Vaccine Coverage**—To model the ages at rotavirus vaccine administration and the rotavirus vaccine coverage achievable with a fully implemented program, we used data on rotavirus vaccine (either RV5 or RV1) and DTaP/diphtheria and tetanus toxoid vaccines from the 2009 National Immunization Survey (NIS; J. Singleton, Immunization Services Division, NCIRD, CDC, written communication, October 2010), which includes information on children born from January 2006 through July 2007.<sup>19</sup> To model the ages at rotavirus vaccine administration in the field, we used the NIS data to estimate the proportion of all first rotavirus vaccine doses given by each week of age during the first year of life, and similarly for doses 2 and 3.<sup>19</sup>

We used data from NIS regarding the DTaP vaccination program (a well-established program)<sup>19</sup> to model rotavirus vaccine coverage under an assumed fully mature vaccine program. We noted, and included in our modeled coverage, that NIS data recorded that some rotavirus doses are being administered after the Advisory Committee on Immunization Practices recommended maximum ages (maximum age first dose: 14 weeks 6 days; maximum age for last dose: 8 months 0 days).<sup>1</sup> Our total assumed coverage for the first dose was 95.8% (90.6% coverage with DTaP dose 1 by age 15 weeks plus 5.2% additional coverage achieved by age 1 year; Table 1). We similarly assumed rotavirus vaccine coverage of 92.6% with dose 2 (92.4% coverage with DTaP dose 2 plus 0.2% additional coverage by age 1 year) and 81.8% coverage with dose 3 (79.8% coverage with DTaP dose 3 plus 2% additional coverage by age 1 year; Table 1).

## Model 2: Benefit–Risk Comparison

We built a second Monte Carlo model, run for 10,000 iterations, to calculate the ratio of the number of deaths, hospitalizations and ED visits averted due to rotavirus vaccination to the number of vaccine-associated intussusception events. We used the probability distributions for vaccine benefits (obtained from model 1), and we built triangular probability distributions of vaccine-associated intussusception, using our calculated coverage from a fully mature vaccination program, baseline intussusception rates in the United States and the relative risk of vaccine-associated intussusception found in Mexico (point estimate, 5.3; details in subsequent sections).<sup>9</sup>

**Baseline Intussusception Rates—**We used hospital and ED discharge databases to calculate the baseline rate of intussusception in US infants. In 90% of intussusception cases in US infants, no underlying cause was identified; we used all cases of intussusception in these databases for our baseline rate calculations.<sup>20</sup> Baseline intussusception hospitalization rates, by week of age during the first year of life, were obtained from the State Inpatient Databases maintained by the Healthcare Cost and Utilization Project.<sup>21</sup> We examined data from 22 states (AZ, CA, CO, CT, FL, GA, HI, IA, IL, KY, MD, KY, MO, NC, NJ, OR, SC, TN, UT, WA, WI, WV) comprising about 67% of the US birth cohort from 2000 through 2005 (prevaccine period). We defined an intussusception hospitalization as a hospitalization with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for intussusception (560.0) listed as a discharge diagnosis, and an intussusception case requiring surgical intervention as one with an ICD-9-CM procedure code of 45.0–48.9 or 54.0–54.2 (abdominal surgery). We calculated the fatality rate among hospitalized intussusception cases by using disposition codes in the database (Table 1).

A study that examined intussusception cases among infants at 3 US children's hospitals before rotavirus vaccine was introduced found that a large proportion of infants with intussusception were classified as being managed only in short-stay (44%) or ED (4%) settings.<sup>22</sup> Therefore, to account for intussusception cases managed in short-stay or ED settings that would not be captured in the Statewide Inpatient Database, we analyzed data from the State Emergency Department Databases using the ICD-9 intussusception code.<sup>23</sup> We used these ED databases from 14 states (CT, GA, HI, IN, MA, MD, MN, MO, NE, NH,

SC, TN, UT, VT), accounting for approximately 20% of the US birth cohort, that provided continuous reports from 2003 through 2005.

The ED databases were not sufficient to calculate rates by week of age during the first year of life of intussusception managed in short-stay or ED settings. Therefore, to estimate baseline rates by week of age of intussusception managed in all care settings combined (inpatient, short-stay and ED), we calculated a single multiplier to apply to the baseline intussusception hospitalization rates by week of age to account for the additional cases in the non-inpatient setting. This multiplier (1.284) was obtained by dividing the average annual intussusception rate from the inpatient and ED databases combined by the average annual rate from the inpatient database alone, among infants aged 6–51 weeks.

**Vaccine-associated Intussusception Risk**—To estimate the number of vaccine-associated intussusception cases, we first determined the baseline number of intussusception cases by week of age that would occur among infants vaccinated with dose 1 if the vaccine had no excess intussusception risk. We determined the number of infants who would receive rotavirus vaccine dose 1 during each week of life, based on our estimates of coverage in a fully implemented program. We then multiplied this number of infants vaccinated during each week of life by the weekly baseline intussusception rate, through 1 year of age. To estimate the total number of intussusception cases (baseline plus excess) that would occur among vaccinated infants if there was an increased risk of intussusception during the first week after dose 1, we multiplied the baseline number of cases during each week of age by the relative risk of vaccine-associated intussusception found in Mexico (point estimate, 5.3).<sup>9</sup> We assumed that this risk occurred only in week 1 after dose 1 of rotavirus vaccine, the risk did not vary by age and there was no excess risk after doses 2 or 3.<sup>9</sup> The cases attributable to vaccine (ie, excess cases) were therefore obtained by subtracting the baseline number of intussusception cases from the total number of cases in vaccinated infants. Excess cases of intussusception that resulted in surgery or death were calculated based on intussusception hospitalizations only, as it was assumed that these outcomes were unlikely to occur in short-stay or ED settings (Table 1).

### Rate of Rotavirus Hospitalization and Rate of Intussusception for an Individual Infant

To estimate the rate of rotavirus hospitalization during the first 5 years of life (per 100,000 children) in the absence of a vaccine program, we used the median number of rotavirus hospitalizations in a birth cohort (obtained from model 1) divided by the number of infants in the birth cohort. To estimate the rate of rotavirus hospitalization for an infant who receives the rotavirus vaccine series, we determined the median number of rotavirus hospitalizations that would occur in a completely vaccinated birth cohort followed to 5 years of age by using 100% coverage for all doses in model 1 and performing a Monte Carlo analysis. This number of rotavirus hospitalizations was then divided by number of infants in the birth cohort. We then estimated the risk of intussusception for an infant without rotavirus vaccine (baseline risk) and with rotavirus vaccine (baseline risk multiplied by 5.3) when aged 8 weeks (the peak week of rotavirus dose 1 administration per NIS data), per 100,000 person-weeks.

## Sensitivity Analysis Using Model 2

We examined the impact of changing the risk of vaccine-associated intussusception on the benefit–risk ratio. We altered the risk of vaccine-associated intussusception within a range (3.0–9.3), and assessed the change in ratio of vaccine-averted rotavirus events (to 5 years of age) to vaccine-associated intussusception events. The range studied is the 95% CI for the risk-ratio estimate from Mexico.<sup>9</sup> For each 0.1 change in excess risk, we calculated the ratios of vaccine-averted rotavirus events per vaccine-associated intussusception event. We then calculated the 95% CIs by using the ratio of the median to the 5th and 95th percentiles for the summary benefit–risk ratio measures (Table 2). This method of calculating CIs will result in slightly different estimates of the CIs than if we had run the Monte Carlo model for each estimate of excess risk.

## RESULTS

### Model 1: Rotavirus Disease Burden With and Without Rotavirus Vaccination

Without a vaccination program, 33 (95% CI: 23–43) rotavirus-associated deaths, 71,175 (95% CI: 50,131–96,802) hospitalizations and 226,126 (95% CI: 157,319–317,685) ED visits would occur in a birth cohort followed to 5 years of age.<sup>15</sup> A fully implemented rotavirus vaccine program would avert 14 (95% CI: 10–19) rotavirus-associated deaths, 53,444 (95% CI: 37,622–72,882) hospitalizations and 169,949 (95% CI: 118,161–238,630) ED visits.

### Model 2: Benefit–Risk Comparison

In the absence of a rotavirus vaccination program, we estimate that 1856 intussusception cases would occur among the birth cohort used in our study during the first year of life. With a fully implemented rotavirus vaccination program, we estimate an additional 58 (range: 27–111) intussusception cases would potentially occur, representing a 3% increase over the baseline number of cases (1856) occurring in the birth cohort during the first year of life. Of the 58 excess intussusception cases, 45 (range: 21–86) would result in hospitalization and 13 (range: 6–25) would be managed in short-stay or ED settings (Tables 2 and 3). Twenty-four of the excess cases (range: 11–45) would require surgery and 0.2 (range: 0.1–0.3) would be fatal. Of the 58 excess intussusception cases, 47 (81%) would occur among infants aged 6–14 weeks, who would receive 94% of the total first doses given to infants in the birth cohort. The 47 excess cases in infants aged 6–14 weeks represent a 32% increase over the baseline number of 147 cases in this age group. Two (5%) excess intussusception cases would occur among infants aged 24–32 weeks; this age window represents 1% of first-dose vaccine recipients.

A fully implemented rotavirus vaccination program would avert a median of 71 (95% CI: 48–112) rotavirus-associated deaths for each intussusception death potentially caused. Further, a median of 1093 (95% CI: 688–1902) rotavirus hospitalizations would be averted for each intussusception hospitalization potentially caused, and 12,115 (95% CI: 7528–21,448) rotavirus ED visits would be prevented for each potential case of intussusception managed in short-stay or ED settings (Table 2). Vaccination would avert a median of 850



(95% CI: 534–1458) rotavirus hospitalizations for each intussusception case potentially caused (cases managed in inpatient, short-stay or ED settings combined).

### Rate of Rotavirus Hospitalization and Intussusception for an Individual Infant

Without a rotavirus vaccine program, a child's rate of rotavirus hospitalization during the first 5 years of life is 1670 per 100,000 children. For a child who has received the vaccine series, the rate of rotavirus hospitalization during the first 5 years of life is 194 per 100,000 children, a decrease of 1476 hospitalizations per 100,000 children. Without rotavirus vaccine, the rate of intussusception during the week for an infant aged 8 weeks is 0.24 per 100,000 infants. For an infant who receives rotavirus vaccine at 8 weeks of age, the rate of intussusception during that week is 1.25 per 100,000 infants, an increase of 1.01 intussusception cases per 100,000 vaccinated infants (Table 4). Overall, based on age distribution for receipt of dose 1 among infants aged 6–14 weeks, the risk translates to approximately 1 excess case of intussusception during week 1 after dose 1 for every 81,000 infants vaccinated at this age.

### Sensitivity Analysis Using Model 2

If the relative risk after dose 1 week 1 was as high as 9.3 (upper limit of the 95% CI from the risk evaluation in Mexico), the summary ratios of rotavirus events averted per intussusception event caused by clinical outcome (death, hospitalization and short-stay or ED visit) are 48, 618 and 6922, respectively (Fig. 1).

## DISCUSSION

If an intussusception risk similar to that seen in Mexico exists in the United States, the number of prevented deaths,<sup>14</sup> hospitalizations (53,444) and ED visits (169,949) from rotavirus disease would substantially exceed the number of deaths (0.2), hospitalizations (45) and short-stay or ED visits (13) due to vaccine-associated intussusception. The benefits of rotavirus vaccine in averted rotavirus disease extend for several years, whereas the excess intussusception risk occurs within the week after the initial dose of rotavirus vaccine, a time when background intussusception rates are low. Thus, the 32% increase over baseline in the number of intussusception cases among infants aged 6–14 weeks translates to a 3% increase in cases among all infants aged <1 year. In comparison, rotavirus hospitalizations among US children aged <5 years would decline by 75% with a fully implemented vaccination program.

For vaccine-associated intussusception risk, we modeled a risk of 5.3 in the week after dose 1 of RV5, based on data from an evaluation of intussusception risk with RV1 vaccination among Mexican infants.<sup>9</sup> This finding was corroborated by an independent manufacturer-led study in Mexico that also found an intussusception risk with the first dose of RV1.<sup>25</sup> A similar observation was also made in Australia, where a vaccine-associated intussusception risk after first RV5 dose and a possible vaccine-associated intussusception risk after RV1 were described in a postlicensure evaluation.<sup>26</sup> It is interesting to note that in Brazil, where an evaluation similar to that in Mexico was conducted, risk of intussusception with dose 1 of RV1 was not observed, but a small increased intussusception risk was found for week 1 after

dose 2 of RV1.<sup>9,25</sup> Because the unique risk pattern seen in Brazil has not been replicated in other settings, we did not model a risk with the second rotavirus vaccine dose.

An intussusception risk associated with rotavirus vaccination has not been documented in the United States. Through August 2010, more than 90% of approximately 35 million doses of rotavirus vaccines distributed in United States were RV5. Neither passive reporting in the Vaccine Adverse Event Reporting System nor active reporting in the Vaccine Safety Datalink<sup>12</sup> has identified an increased intussusception risk associated with RV5. However, available data are insufficient to exclude the level of risk seen with RV5 in Australia,<sup>11–14</sup> and both Vaccine Adverse Event Reporting System and Vaccine Safety Datalink have limited data on RV1. Therefore, healthcare providers should maintain increased vigilance for intussusception in the first week after the first dose of rotavirus vaccine and inform caretakers of early signs and symptoms of intussusception.

Data on timing of administration of rotavirus vaccine doses is critical for our modeling, given the substantial increase in baseline intussusception rates by week of age in the first few months of life. We used the NIS for nationally representative data on the timing of RV dose 1, available for children born during 2006 to 2007. It is reassuring that these data were very similar to the data on timing of rotavirus vaccine dose 1 for children born in 2009, obtained from 8 sentinel Immunization Information System sites.<sup>27</sup>

Limitations of our study include basing prevaccine rotavirus disease burden data on all-cause gastroenteritis estimates. Although population based, these data may be biased by year-to-year variability in the epidemiology of other gastroenteritis etiologies and unmeasured time-dependent trends (eg, changes in ICD-9 coding practices). Additionally, published vaccine effectiveness data for partial immunization schedules are limited and some estimates were interpolated from available data. Published data on vaccine effectiveness beyond 3 years of age are unavailable; however, most severe rotavirus disease occurs by this age, so we assumed no waning of vaccine efficacy in our model. Our model did not include the impact of vaccination on outpatient visits or the societal benefits of vaccination, and thus our estimate of vaccination benefits was conservative. Furthermore, recent data demonstrate that there have been rotavirus disease reductions in age cohorts that are ineligible for vaccination (ie, herd immunity effects).<sup>28–30</sup> However, to again be conservative, indirect benefits of rotavirus vaccine were not included in our model.

The burden of severe rotavirus disease averted due to vaccination compared with the vaccine-associated intussusception events offers a side-by-side analysis of the benefits and potential risks. Despite the greater severity of most intussusception hospitalizations compared with rotavirus hospitalizations, the summary benefit–risk ratios for death and hospitalization of 71:1 and 1093:1, respectively, make an argument favoring vaccination. For an individual child, decisions about vaccine benefits and risk should be made by informed parents and providers. From a public health perspective, our analysis shows that the number of deaths, hospitalizations and ED visits averted by vaccination are greater than those potentially caused by intussusception risk.



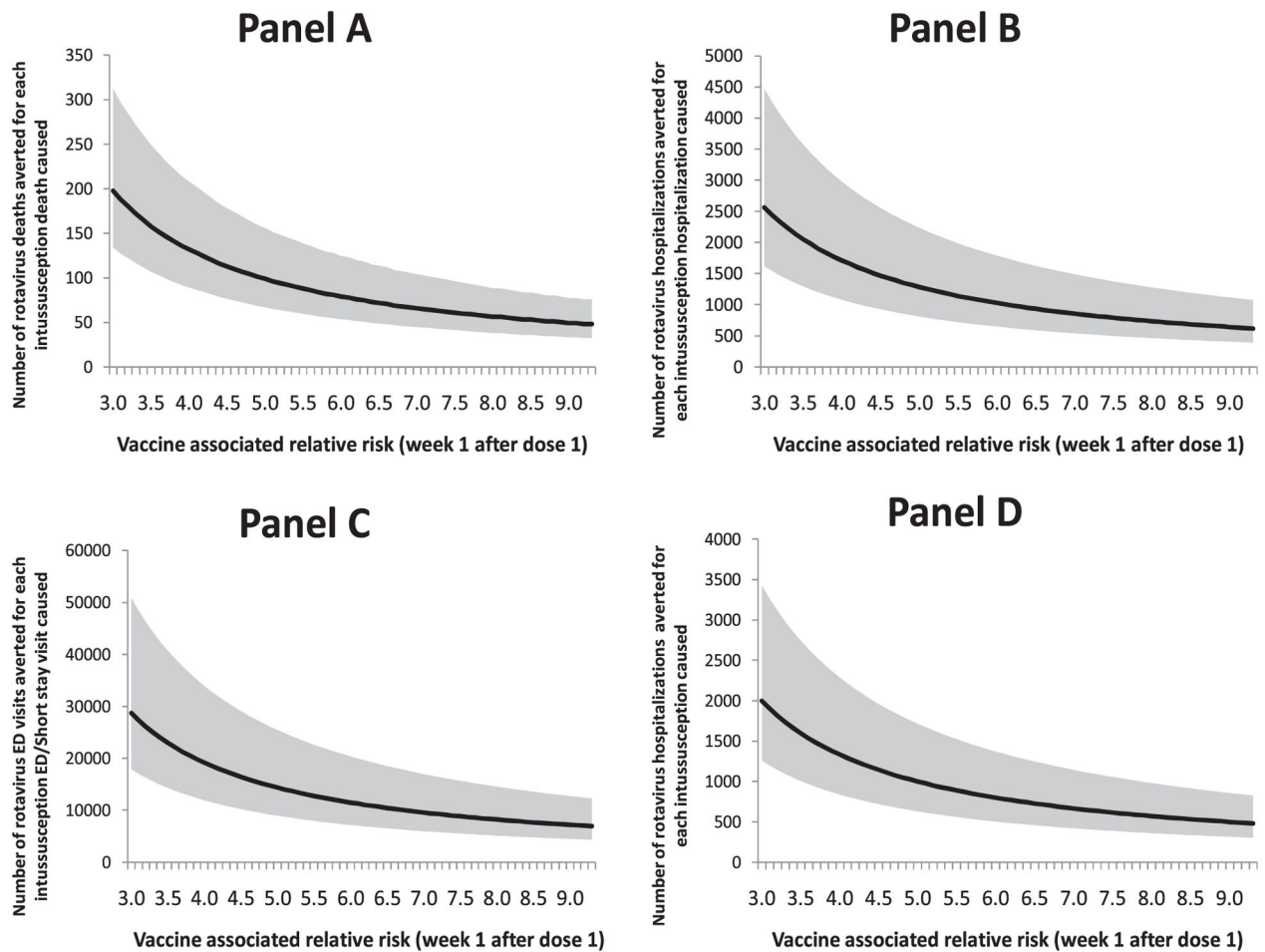
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**FIGURE 1.**

The number of rotavirus events averted (to age 5 years) per each intussusception event potentially caused by rotavirus vaccine, with varying levels of vaccine-associated intussusception risk (in the 1 week after dose 1 of vaccine). A, Rotavirus-associated deaths averted per intussusception death potentially caused. B, Rotavirus-associated hospitalizations averted per intussusception hospitalization potentially caused. C, Rotavirus-associated ED visits averted per intussusception case managed in short-stay or ED settings. D, Rotavirus-associated hospitalizations averted per intussusception case (managed in inpatient, short-stay or ED settings combined) potentially caused. The median values (solid black lines) are calculated using the median estimates of benefits (events averted, Table 2, column 2). The 95% CIs (shaded gray area) were calculated using the ratio of the median to the 5th and 95th percentiles for the summary benefit risk ratio measures (Table 2). This method will result in slightly different estimates of the medians and CIs than if we had run the Monte Carlo model for each estimate of excess risk.

**TABLE 1**

Model Input Variables for Birth Cohort and Vaccine Coverage, Intussusception Risk and Vaccine Effectiveness

Model Inputs	Variable	Point Estimate	95% CIs	Reference
Birth cohort and vaccine coverage	Number of 2009 live births	4,261,494	—	1
	Proportion of birth cohort vaccinated with rotavirus vaccine dose 1	95.8%	—	2
	Proportion of birth cohort vaccinated with rotavirus vaccine dose 2	92.7%	—	2
	Proportion of birth cohort vaccinated with rotavirus vaccine dose 3	81.8%	—	2
Potential rotavirus vaccine intussusception risk	Excess risk of intussusception in week 1 after dose 1 of rotavirus vaccine	5.3	3.0–9.3	3
	Percent of intussusception hospitalizations requiring surgery	52.8%	51.1–55.4% *	4
	Percent of intussusception hospitalizations resulting in death	0.3%	0–0.5% *	4
	Vaccine effectiveness for rotavirus hospitalization/death - 1 dose	66%	16–86%	5
Rotavirus vaccine effectiveness	Vaccine effectiveness for rotavirus hospitalization/death—2 doses	90%	75–96%	5
	Vaccine effectiveness for rotavirus hospitalization/death—3 doses	92%	86–96%	5
	Vaccine effectiveness for rotavirus ED visits—1 dose	55%	5–75% *	NA
	Vaccine effectiveness for rotavirus ED visits—2 doses	79%	64–85% *	NA
	Vaccine effectiveness for rotavirus ED visits—3 doses	81%	52–92%	5

\* Ranges presented instead of confidence intervals.

CIs indicates confidence intervals; NA, not applicable.

**TABLE 2**

Benefits and Potential Risks of a Rotavirus Vaccine Program: Deaths, Hospitalizations and Emergency Department Visits in 1 Birth Cohort Followed to Age 5

Events	Benefits	Risks	Benefit–risk Ratio <sup>‡§</sup>
	Rotavirus-associated Sequelae Averted <sup>*</sup>	Excess Intussusception Cases and Sequelae <sup>‡</sup>	
Deaths	14 (10–19)	0.2 (0.1–0.3)	71 (48–112)
Hospitalizations	53,444 (37,622–72,882)	45 (21–86)	1093 (688–1902) <sup>¶</sup>
Emergency department visits	169,949 (118,161–238,630)	13 (6–25)	12,115 (7528–21,448)

Assuming rotavirus vaccine coverage in Table 1 (1st dose—95.8%, 2nd dose—92.7% and 3rd dose—81.8%).

<sup>\*</sup> 5–95% confidence limits based upon the vaccine effectiveness 5–95% limits or range.

<sup>‡</sup> Range based on the 5–95% limits of the vaccine-associated intussusception relative risk estimate.

<sup>‡</sup> Point estimates (rotavirus outcomes averted per each intussusception outcome potentially caused) and 5–95% confidence limits based upon the median and 5–95% distributions obtained from 10,000 Monte Carlo simulations sampling from the benefits and risks for each clinical setting.

<sup>§</sup> The ratio of median benefit–risk ratio to the 5th and 95th percentile for deaths was 0.68 and 1.58, for hospitalizations was 0.63 and 1.74 and for ED visits was 0.62 and 1.77 (Fig. 1).

<sup>¶</sup> Median benefit–risk ratio for rotavirus hospitalizations averted per each intussusception case (managed in inpatient, short-stay or ED settings combined) potentially caused is 850 (95% CI: 534–1458).

TABLE 3

Intussusception Events at Baseline and Number of Excess Cases Potentially Due to a Rotavirus Vaccination Program by Infant Age Group Per Year

Infant Age (weeks)	Number of Infants Vaccinated With Dose 1 of Vaccine (% of Birth Cohort)	Baseline		With Rotavirus Vaccine*		Excess Intussusception Events per Birth Cohort
		Intussusception Event Rate <sup>†</sup>	Total Intussusception Events <sup>‡,§</sup>	Intussusception Event Rate <sup>¶</sup>	Total Intussusception Events <sup>‡,  </sup>	
0–5	29,194 (0.7)	4	19	20 (11–35)	19 (19–19)	0 (0–0)
6–8**	1,912,219 (44.9)	10	24	53 (30–92)	43 (33–60)	18 (9–36)
9–11**	1,707,852 (40.1)	19	46	100 (57–175)	70 (57–92)	24 (11–46)
12–14**	211,657 (5.0)	31	76	165 (93–289)	82 (79–86)	5 (2–10)
15–23	171,932 (4.0)	54	400	287 (163–504)	407 (403–414)	7 (3–14)
24–32	41,264 (1.0)	70	514	370 (209–649)	517 (515–519)	2 (1–5)
33–41	0 (0)	62	454	326 (185–572)	454 (454–454)	0 (0–0)
42–51	6877 (0.2)	39	323	209 (118–366)	323 (323–323)	0 (0–1)
			1856		1914 (1883–1967) <sup>††</sup>	58 (27–111) <sup>††</sup>

\* Range based on the 5–95% limits (3.0–9.3) of the rotavirus vaccine-associated intussusception relative risk estimate (5.3).

<sup>†</sup> Average intussusception rate for infants in each age category, per 100,000 person-years.<sup>‡</sup> Based on a birth cohort of 4,261,494 infants (size of 2009 birth cohort).<sup>§</sup> Total intussusception events represent the sum of events that occur within each age category and are based on weekly intussusception event rates at baseline (no vaccine).<sup>¶</sup> Average rates per 100,000 vaccinated person-years, which apply only to infants in week 1 after dose 1 within each age category.<sup>||</sup> Based on the formula:  $(N_V \times R_V) + (N_0 \times R_0)$ .  $N_V$  indicates number of infants receiving dose 1 at that age;  $R_V$ , intussusception event rate among vaccinated infants;  $N_0$ , number of infants not receiving dose 1 at that age;  $R_0$ , intussusception event rate among unvaccinated infants.

\*\* ACIP recommended age for administration of rotavirus vaccine dose 1.

<sup>††</sup> Total events differ slightly from sum of events presented in individual strata because of rounding.

ACIP indicates Advisory Committee on Immunization Programs.



**TABLE 4**

Rates of Rotavirus Hospitalization and Intussusception for an Individual Infant With and Without Rotavirus Vaccine

	Rate Without Rotavirus Vaccine	Rate With Rotavirus Vaccine	Rate Difference
Rotavirus gastroenteritis hospitalization rate (to age 5 years) <sup>*</sup>	1670 per 100,000 <sup>†</sup>	194 per 100,000 <sup>‡</sup>	Decreased by 1476 per 100,000
Intussusception rate (for 1 week period) <sup>§</sup>	0.24 per 100,000	1.25 per 100,000 <sup>¶</sup>	Increased by 1.01 per 100,000 <sup>//</sup>

<sup>\*</sup> Rate per 100,000 children aged <5 years.

<sup>†</sup> This rotavirus hospitalization rate is based on the median value of rotavirus hospitalizations (71,175) in 1 birth cohort, obtained from 10,000 Monte Carlo simulations when the model included no rotavirus vaccination.

<sup>‡</sup> This rotavirus hospitalization rate is based on the median value rotavirus hospitalizations (8263) in 1 birth cohort, obtained from 10,000 Monte Carlo simulations when the model included 100% coverage with all 3 rotavirus vaccine doses.

<sup>§</sup> Includes all intussusception cases managed in inpatient, short-stay or ED settings combined. Rate expressed per 100,000 person-weeks in infants aged 8 weeks.

<sup>¶</sup> Assuming that rotavirus vaccine dose 1 given at age 8 weeks, the peak age for rotavirus dose 1 administration.

<sup>//</sup> Per 100,000 infants who receive dose 1 at age 8 weeks. Overall, based on age distribution for receipt of dose 1 among infants aged 6–14 weeks, rate translates to approximately 1 excess case of intussusception during the week after the first dose for every 81,000 infants vaccinated at this age.